FILED IN DUPLICATE

525 Rec'd PCT/PTO 16 NOV 2000

FORM PTO-1390 (Modified) (REV 11-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: **30394-1041**

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.5): **09/700669**

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/NL99/00316	**20 May 1999**	**20 May 1998**

TITLE OF INVENTION

USE OF A NUCLEIC ACID-BINDING CHEMOTHERAPEUTIC AGENT, AND A PHARMACEUTICAL COMPOSITION

APPLICANT(S) FOR DO/EO/US

Bernt Sweder VAN ASBECK and
Johannes Josephus Maria MARX

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☒ Certificate of Mailing by Express Mail
20. ☒ Other items or information:

Unsigned Declaration and Power of Attorney for Patent Application
Associate Power of Attorney

PCTUS1/REV03

U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR 1.5)	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
09/700669	PCT/NL99/00316	30394-1041

21. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐ Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO	$1,000.00	
☒ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but Internation Search Report prepared by the EPO or JPO	$860.00	
☐ International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO	$710.00	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4)	$690.00	
☐ International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4)	$100.00	
ENTER APPROPRIATE BASIC FEE AMOUNT =		$860.00
Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).		$0.00

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	7 - 20 =	0	x $18.00	$0.00
Independent claims	2 - 3 =	0	x $80.00	$0.00
Multiple Dependent Claims **(check if applicable)**.			☐	$0.00
TOTAL OF ABOVE CALCULATIONS =				$860.00
Reduction of 1/2 for filing by small entity, if applicable. ~~Verified Small Entity Statement must also be filed~~ (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable).**			☒	$430.00
SUBTOTAL =				$430.00
Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)).			+	$0.00
TOTAL NATIONAL FEE =				$430.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).**			☐	$0.00
TOTAL FEES ENCLOSED =				$430.00
			Amount to be: refunded	$
			charged	$

☒ A check in the amount of **$430.00** to cover the above fees is enclosed.

☐ Please charge my Deposit Account No. in the amount of to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **13-4213** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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SIGNATURE

Jeffrey D. Myers
NAME

35,964
REGISTRATION NUMBER

16 November 2000
DATE

PATENT APPLICATION

I hereby certify that this paper is being deposited with the United States Postal Service on **16 November 2000**, in an envelope as "Express Mail Post Office to Addressee" mailing Label No. **EL675081260US** addressed to Box PCT, Commissioner for Patents, Washington, D.C. 20231.

Annette M. Turk, Legal Assistant

16 November 2000
(Date)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Bernt Sweder VAN ASBECK
and Johannes Josephus Maria MARX

Serial No.: UNKNOWN

Examiner: UNKNOWN

Priority claimed to PCT/NL99/00316

Filed: Herewith (16 November 2000)

Group Art Unit: UNKNOWN

For: USE OF A NUCLEIC ACID-BINDING CHEMOTHERAPEUTIC AGENT, AND A PHARMACEUTICAL COMPOSITION

FIRST PRELIMINARY AMENDMENT

Box: PCT
Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend the application, without prejudice, as follows:

In the Claims:

Please cancel claims 1-6 and add the following claims:

--7. A method of treatment of a disease caused by virions, comprising administering a nucleic acid-binding chemotherapeutic which complexes a metal ion, thereby yielding a complex that promotes formation of hydroxyl radicals from hydrogen peroxide.

--7. A method of treatment of a disease caused by virions, comprising administering a nucleic acid-binding chemotherapeutic which complexes a metal ion, thereby yielding a complex that promotes formation of hydroxyl radicals from hydrogen peroxide.

8. A method according to claim 7 wherein the nucleic acid-binding chemotherapeutic agent is selected from the group comprising bleomycin, adriamycin, and their derivatives.

9. A method according to claim 8 wherein the nucleic acid-binding chemotherapeutic agent is used for the treatment of a disease caused by an RNA virus.

10. A method according to claim 9 wherein the nucleic acid-binding chemotherapeutic agent is used for the treatment of a disease caused by HIV.

11. A pharmaceutical composition comprising: a nucleic acid-binding chemotherapeutic agent comprising a metal ion complexed therewith, which complex promotes the formation of hydroxyl radicals from hydrogen peroxide *in vivo*; and a pharmaceutically acceptable carrier or excipient, which comprises an iron-chelating compound which binds iron in a form in which such chelated iron is unable to promote the formation of hydroxyl radicals from hydrogen peroxide.

12. A pharmaceutical combination composition according to claim 11 wherein the iron-chelating compound has an iron-chelating capacity which is at least three times lower than that of the nucleic acid-binding chemotherapeutic agent.

13. A pharmaceutical combination composition according to claim 11 wherein the iron-chelating compound has an iron-chelating capacity which is at least ten times lower than that of the nucleic acid-binding chemotherapeutic agent.--

REMARKS

The foregoing amendment to the claims is being offered in a format acceptable to the U.S. Patent and Trademark Office. No new matter is presented by this Amendment. Entry of this amendment by the Examiner is respectfully requested.

Authorization is given to charge payment of any fees required, or credit any overpayment, to Deposit Acct. 13-4213.

Respectfully submitted,

Dated: 16 November 2000

By: ______________________

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Use of a nucleic acid-binding chemotherapeutic agent, and a pharmaceutical composition

The present invention relates to a use of a nucleic acid-binding chemotherapeutic agent, wherein the nucleic acid-binding chemotherapeutic agent is capable of complexing a metal ion, yielding a complex that promotes the formation of hydroxyl radicals from hydrogen peroxide.

Such a nucleic acid-binding chemotherapeutic agent is already known in the art. For example, certain neoplastic tissues (tumours) may be treated with bleomycin. Bleomycin is capable of binding bivalent iron, while the ferro-ion retains its ability to promote the formation of hydroxyl radicals from hydrogen peroxide.

It is the object of the present invention to provide a novel use of a nucleic acid-binding chemotherapeutic agent such as defined above.

According to the present invention the nucleic acid-binding chemotherapeutic agent can be used for the preparation of a pharmaceutical composition for the treatment of a disease caused by virions.

Surprisingly it has been found that by applying the above-defined nucleic acid-binding chemotherapeutic agent, the virus replication may be inhibited, without visible detriment to the host cell. Without being bound to any theory, applicant believes that the inhibition is specific because the formation of hydroxyl radicals from hydrogen peroxide is promoted especially in virus-infected cells.

According to a preferred embodiment, the nucleic acid-binding chemotherapeutic agent is selected from the group comprising bleomycin, adriamycin, and their derivatives.

These compounds possess excellent metal ion-complexing properties. In particular, they are capable of binding ferro-ions in the body of a patient. This enables the ferrobleomycin complex that is formed to promote the formation of hydroxyl radicals from hydrogen peroxide.

Preferably the nucleic acid-binding chemotherapeutic agent is used for the preparation of a pharmaceutical composition for the treatment of a disease caused by an RNA virus replication-inhibiting agent, in particular the nucleic acid-binding chemotherapeutic agent is used for the preparation of a pharmaceutical composition for the treatment of a disease caused by a HIV.

Carter, B.J. et al. (Proc. Natl. Acad. Sci. USA, volume 87, pp. 9373-9377 (1990)) describe the effect of Fe(II)-bleomycin complex on mRNA which codes for reverse transcriptase of HIV-1. The experiment described was performed in a cell-free system. There is no indication that the formation of hydroxyl radicals from hydrogen peroxide is promoted preferentially in infected cells.

The invention further relates to a pharmaceutical combination composition comprising a nucleic acid-binding chemotherapeutic agent comprising a metal ion complexed therewith, which complex is able to promote the formation of hydroxyl radicals from hydrogen peroxide, together with a pharmaceutically acceptable carrier or excipient, and which also comprises an iron-chelating compound which binds iron in a form in which it is unable to promote the formation of hydroxyl radicals from hydrogen peroxide.

Such an iron-chelator combination which optionally comprises two separate pharmaceutical compositions, each of which possessing one of the respective active components, facilitates more specific localization of the formation of the hydroxyl radicals. By using an iron-chelating compound that is unable to penetrate the cells, it is possible to preferentially prevent the formation of ferro-bleomycin complex outside the cells, and consequently also to reduce the damage that such a complex causes. At the same time, the use of an iron-chelating compound that is able to penetrate the cells, will limit the amount of ferro-ions that limit the formation of hydroxyl radicals. In this way at least part of the activation process of the transcription factor *Nuclear Factor kappa B* (NFκB), that can stimulate virus replication may be limited in the

cytoplasm. However, it is necessary to ensure that iron is available for bleomycin. A physician may achieve this by choosing suitable doses of both active components, depending on the body weight of the person to the treated, and the person's available iron level. According to a favour-

able embodiment an iron-chelating compound is chosen having an iron-chelating capacity which is preferably at least three times lower, more preferably at least ten times lower than that of the nucleic acid-binding chemotherapeutic agent.

Due to the greater affinity of bleomycin for iron, it is thus possible to promote the presence of active ferrobleomycin complex in infected cells and, in particular, to limit the extracelluar detrimental effects of bleomycin complex.

Applicant considers the possibility that the use of an iron-chelating compound as defined above may also be applied to limit undesired damage occurring during the treatment of neoplastic tissues with a nucleic acid-binding chemotherapeutic agent such as bleomycin.

The present invention will now be exemplified by way of example and with reference to the drawing in which

Fig. 1 shows a graph representing the effect of bleomycin on the HIV-1 replication in macrophages;

Fig. 2 shows a graph representing the site of toxicity of bleomycin for macrophages;

Fig. 3 shows a graph representing the effect of bleomycin on the HIV-1 replication in lymphocytes;

Fig. 4 shows a graph representing the effect of the bleomycin concentration on the lymphocyte proliferation.

Example

Macrophages and lymphocytes (10^6 cells/ml) were infected with HIV-1_{Ba-L} for two hours. The ratio HIV particles/number of cells was 0.005 for macrophages and 0.001 for lymphocytes. The infected cells were then washed twice in order to remove excess virus. The cells were incubated for five days in RPMI 1640 medium (supplemented with 10% foetal calf serum, 10 U/ml of IL-2, 10 μg/ml of gentamycin, and 0.5 μg/ml of ciprofloxamine) with 3 iron chelators, being Deferoxamine (DI; Novartis Pharma, Arnhem, the Netherlands), Deferiprone (L1; Duchefa Farma B.V., Haarlem, the Netherlands) or Bleomycin (BLM; H. Lundbeck A/S, Copenhagen, Denmark). Virus in culture supernatant

was inactivated with Empigen (Calbiochem-Novabiochem Co., La Jolla, California, United States of America) in a final concentration of 0.05% and subsequently heated for 30 minutes at 56°C. The p24 concentration was determined in an ELISA, as measure for the replication of HIV-1 (Moore, J.P. et al., Science 250, pp. 1139-1142 (1990)). Cytotoxicity measurements were carried out using a fluorescence-activated cell sorter with the aid of colouring with propidium iodide and DiOC5 (3,3'-diapentiloxacarboxyl amine iodide). The proliferation of lymphocytes was measured by incorporation of ^{3}H-thymidine. Figure 1 and Figure 2 show the dose-dependent reduction of the HIV-1 replication. The limited cytotoxicity of bleomycin for macrophages is appears from Figure 3. The insignificant effect of bleomycin on the proliferation of lymphocytes is shown in Figure 4. In contrast with DF and L1 which do inhibit cell proliferation (results not shown; L1 inhibits the proliferation substantially completely at 10 μM), the cell proliferation with bleomycin remains intact over a wide concentration range; this fact indicates that another mechanism which is not based on the inhibition of proliferation, is involved. Likewise, the BLM-induced reduction of HIV replication is not a result of cytotoxic effects of BLM.

In an attempt to find out more about the level at which the nucleic acid-binding chemotherapeutic agent is activated to reduce the number of virions in an infected cell, the transcription factors present on HIV-LTR (HIV-Long Terminal Repeat) have been studied, of which NFκB plays an important role in viral transcription. For the initiation of the transcription of pro-viral DNA present in the host genome, it is necessary that NFκB is present. EMSE analysis (Electrophoretic Mobility Shift Assay) of NFκB in nuclear extracts showed that bleomycin has no effect on NFκB activation, suggesting that HIV inhibition due to bleomycin occurs along a path other than transcription inhibition. The fact that NFκB prepared from nuclear extract prepared from Jurkat cells stimulated with 20 ng/ml phorbol myristatic acetate (PMA) were not inhibited by BLM (concentrations up to 3 μg/ml), suggests that the

inhibition of HIV-1 by BLM occurs in another manner than that proposed for conventional iron chelators such as DF (Sappey et al. Aids Res. Hum. Retroviruses 11, pp 1049-1061 (1995)).

In order to see whether bleomycin is active at an earlier stage, i.e. before integration into the genome, the viral DNA-damaging properties of BLM in peripheral blood lymphocytes (PBL) infected with HIV-1 were examined. To this end the products of reverse transcription, among which was the first minus strand strong stop DNA, were amplified using the R/U5 primers: sense 5'-GGCTAACTAGGGAA-CCCACTG-3' and antisense 5'-CTGCTAGAGATTTTCCACACTGAC-3' (biotinylated at 5' end), which resulted in a fragment of 140 bp. To quantify this fragment, a digoxigenin-labelled probe 5'-TGTGTGCCCGTCTGTTGTGTG-3' was used. Quantification was carried out with the aid of a DIG detection ELISA (Boehringer-Mannheim, Mannheim, Germany). After incubation with BLM, strong stop DNA which was formed in peripheral blood lymphocytes (PBL) infected with HIV, was virtually absent. This could either mean that the reverse transcriptase enzyme is inhibited, or that the DNA products of reverse transcriptase are damaged by BLM directly.

Based on experiments that have been carried out, it is believed that bleomycin damages viral DNA and/or RNA in the cytoplasm. The GAPDH-DNA concentration in the cell measured as control (GAPDH stands for glyceraldehyde-3-phosphate dehydrogenase) remains substantially constant, supporting the idea that the host DNA is fairly well protected against BLM, and that BLM preferably attacks DNA/RNA in the cytosol, in this case viral DNA/RNA. This could also explain why in the first experiment described above, the p24 values, after incubation of the cells with BLM, were not reduced completely. After all, as the cells are incubated in the absence of BLM for 2 hours, some proviral integration into the host genome will undoubtedly have occurred.

EE

CLAIMS

1. A use of a nucleic acid-binding chemotherapeutic agent for the preparation of a pharmaceutical composition for the treatment of a disease caused by virions, wherein the nucleic acid-binding chemotherapeutic agent is capable of complexing a metal ion, yielding a complex that promotes the formation of hydroxyl radicals from hydrogen peroxide.

2. A use according to claim 1, **characterized** in that the nucleic acid-binding chemotherapeutic agent is selected from the group comprising bleomycin, adriamycin, and their derivatives.

3. A use according to claim 1 or 2, **characterized** in that the nucleic acid-binding chemotherapeutic agent is used for the preparation of a pharmaceutical composition for the treatment of a disease caused by an RNA virus.

4. A use according to claim 3, **characterized** in that the nucleic acid-binding chemotherapeutic agent is used for the preparation of a pharmaceutical composition for the treatment of a disease caused by a HIV.

5. A pharmaceutical combination composition comprising a nucleic acid-binding chemotherapeutic agent comprising a metal ion complexed therewith, which complex is able to promote the formation of hydroxyl radicals from hydrogen peroxide, together with a pharmaceutically acceptable carrier or excipient, and which also comprises an iron-chelating compound which binds iron in a form in which it is unable to promote the formation of hydroxyl radicals from hydrogen peroxide.

6. A pharmaceutical combination composition according to claim 5, **characterized** in that iron-chelating compound has an iron-chelating capacity which is preferably at least three times lower, more preferably at least ten times lower than that of the nucleic acid-binding chemotherapeutic agent.

PATENT APPLICATION

I hereby certify that this paper is being deposited with the United States Postal Service on **16 November 2000**, in an envelope as "Express Mail Post Office to Addressee" mailing Label No. **EL675081260US** addressed to Box PCT, Commissioner for Patents, Washington, D.C. 20231.

Annette M. Turk, Legal Assistant

16 November 2000
(Date)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Bernt Sweder VAN ASBECK
and Johannes Josephus Maria MARX

Serial No.: UNKNOWN

Examiner: UNKNOWN

Priority claimed to PCT/NL99/00316

Filed: Herewith (16 November 2000)

Group Art Unit: UNKNOWN

For: USE OF A NUCLEIC ACID-BINDING CHEMOTHERAPEUTIC AGENT, AND A PHARMACEUTICAL COMPOSITION

ASSOCIATE POWER OF ATTORNEY

Box: PCT
Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Jeffrey D. Myers, a principal attorney in the above-identified application for Letters Patent, hereby appoints:

Deborah A. Peacock, Reg. No. 31,649
Paul Adams, Reg. No. 21,096
Rod D. Baker, Reg. No. 35,434
Brian J. Pangrle, Reg. No. 42,973
Andrea L. Mays, Reg. No. 43,721; and
Stephen A. Slusher, Reg. No. 43,924

as associate attorneys with full power.

Respectfully submitted,

Date: 16 November 2000

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[\\JDM\DOCS\ANNETTE\Los&Stigter-APOA.PTO.doc] 30394-1041

Docket No.
30394-1041

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled
USE OF A NUCLEIC ACID-BINDING CHEMOTHERAPEUTIC AGENT, AND A PHARMACEUTICAL COMPOSITION

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on **16 November 2000** as United States Application No. or PCT International Application Number **09/ 700,669**

and was amended on _____
(if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, Section 1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, Section 119(a)-(d) or Section 365(b) of any foreign application(s) for patent or inventor's certificate, or Section 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
NL 100226	**Netherlands**	**20 May 1998**	☐
(Number)	(Country)	(Day/Month/Year Filed)	
PCT/NL99/00316	**PCT**	**20 May 1999**	☐
(Number)	(Country)	(Day/Month/Year Filed)	
			☐
(Number)	(Country)	(Day/Month/Year Filed)	

I hereby claim the benefit under 35 U.S.C. Section 119(e) of any United States provisional

(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)
(Application Serial No.)	(Filing Date)

I hereby claim the benefit under 35 U. S. C. Section 120 of any United States application(s), or Section 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. Section 112, I acknowledge the duty to disclose to the United States Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, C. F. R., Section 1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

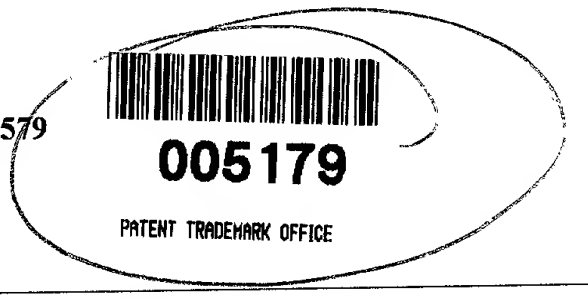
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith. *(list name and registration number)*

JEFFREY D. MYERS, Reg. No. 35,964

Send Correspondence to: **CUSTOMER NO. 001579**



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